

FIELD OF THE INVENTION

This invention relates to a novel thiazole derivative which is useful as a fungicide.

5 BACKGROUND OF THE INVENTION

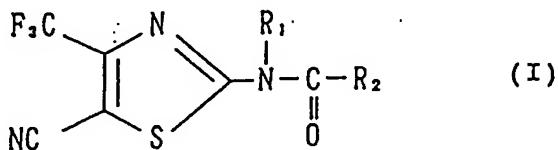
The high agricultural productivity of today is ensured by the application of fertilizers, agricultural chemicals and various farm materials.

On the other hand, continuous application of agricultural chemicals causes a serious problem, namely, 10 the appearance of chemical-resistant strains. Therefore, it has been urgently required to develop novel compounds which are useful as a fungicide. It is an object of the present invention to provide a novel thiazole derivative having a fungicidal action.

SUMMARY OF THE INVENTION

15 The present inventors have conducted extensive studies in order to develop a novel compound having a fungicidal action and, as a result, completed the present invention.

Accordingly, the present invention provides a thiazole derivative represented by the following formula (I):



wherein R₁ represents a hydrogen atom or an alkyl group; and R₂ represents a phenyl group, a substituted phenyl group, a benzyl group, a substituted benzyl group, a phenylalkyl group, a naphthyl group, an alkyl group, a cycloalkyl group, a substituted alkyl group, an alkenyl group, an alkynyl group, a furyl group, a thieryl group, a 5-membered heterocyclic ring containing 1 to 3 nitrogen atoms in the ring and a 6-membered heterocyclic ring containing 1 to 3 nitrogen atoms in the ring; provided that when the 5-membered heterocyclic ring or the 6-membered heterocyclic ring contains one or two nitrogen atom, the remaining atoms in the ring are all carbon atoms or a combination of carbon atoms with one oxygen atom or one sulfur atom; and further provided that the furyl group, the thieryl group, the 5-membered heterocyclic ring and the 6-membered heterocyclic ring may be substituted by one to three substituents selected from an alkyl group, an alkoxy group, a halogen atom and a haloalkyl group; and a fungicide composition comprising the thiazole derivative represented by formula (I) as an active ingredient, and a carrier.

40 DETAILED DESCRIPTION OF THE INVENTION

The alkyl group represented by R₁ in formula (I) contains from 1 to 6 carbon atoms, preferably from 1 to 4 carbon atoms. Specific examples thereof include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl and t-butyl groups. Among them, methyl group is preferred.

The phenylalkyl group represented by R₂ in formula (I) contains from 7 to 15 carbon atoms, preferably from 7 to 11 carbon atoms. Specific examples thereof include 1-phenylethyl, 1-phenyl-1-methylethyl, 1-phenylpropyl, 1-phenyl-1-methylpropyl, 1-phenylbutyl, 1-phenylpentyl, 1-phenyl-1-methylbutyl and 1-phenyl-1-ethylpropyl groups. Among them, 1-phenylethyl and 1-phenyl-1-methylethyl groups are preferred.

50 The alkyl group represented by R₂ in formula (I) contains from 1 to 10 carbon atoms, preferably from 1 to 8 carbon atoms. Specific examples thereof include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, n-hexyl, n-heptyl and n-octyl groups. Among them, methyl, ethyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl and n-hexyl groups are preferred.

The cycloalkyl group represented by R₂ in formula (I) contains from 3 to 8 carbon atoms, preferably from 3 to 6 carbon atoms. Specific examples thereof include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. Among them, cyclopropyl and cyclopentyl groups are preferred.

The alkenyl group represented by R₂ in formula (I) contains from 2 to 8 carbon atoms, preferably from 2 to 6 carbon atoms. Specific examples thereof include vinyl, allyl, butenyl, pentenyl and hexenyl groups.

Among them, allyl group is preferred.

The alkynyl group represented by R_2 in formula (I) contains from 2 to 8 carbon atoms, preferably from 2 to 6 carbon atoms. Specific examples thereof include ethynyl, propynyl, butynyl, pentynyl and hexynyl groups. Among them, butyl group is preferred.

5 Specific examples of the 5-membered heterocyclic ring containing 1 to 3 nitrogen atoms in the ring represented by R_2 in formula (I) include pyrrole, pyrrolidine, oxazole, isoxazole, thiazole, isothiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine and triazole. Among them, pyrrole and pyrazole are preferred.

10 Specific examples of the 6-membered heterocyclic ring containing 1 to 3 nitrogen atoms in the ring represented by R_2 in formula (I) include pyridine, oxazine, pyridazine, piperazine, morpholine, pyrimidine, pyrazine, oxadiazine, thiadiazine and triazine groups. Among them, pyridine and pyrazine groups are preferred.

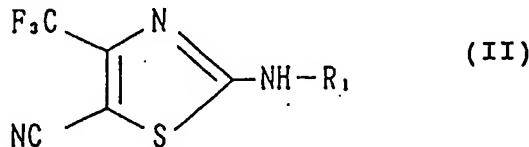
15 Examples of the substituent of the substituted phenyl, substituted benzyl and substituted alkyl groups represented by R_2 in formula (I) include halogen atoms (e.g., fluorine, chlorine, bromine, iodine) and hydroxyl, nitro, cyano, alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl), alkoxy (e.g., methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, t-butoxy), alkylcarbonyl (e.g., acetyl, propionyl, n-butyryl, i-butyryl), alkoxy carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, i-propoxycarbonyl), alkylcarbonyloxy (e.g., acetoxy, propionyloxy, n-butyryloxy, i-butyryloxy), alkylamino (e.g., methylamino, ethylamino, propylamino, i-propylamino, n-butylamino, i-butylamino, t-butylamino, 20 dimethylamino, methylethylamino, diethylamino, methylpropylamino), haloalkyl (e.g., trifluoromethyl, trichloromethyl, trifluoroethyl, trichloroethyl), haloalkoxy (e.g., trifluoromethoxy, trifluoroethoxy, trichloromethoxy, trichloroethoxy), alkylthio (e.g., methylthio, ethylthio, propylthio, i-propylthio, butylthio, i-butylthio, t-butylthio), alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, propylsulfonyl, i-propylsulfonyl, butylsulfonyl, i-butylsulfonyl, t-butylsulfonyl), alkoxy carbonylalkoxy (e.g., ethoxycarbonylmethoxy) and alkenyl (e.g., vinyl, allyl, 25 butenyl), each containing 1 to 6 carbon atoms, preferably from 1 to 4 carbon atoms. Among them, methyl, ethyl, t-butyl, hydroxyl, methoxy, acetyl, methoxycarbonyl, acetoxy, nitro, dimethylamino, cyano, trifluoromethyl, trifluoromethoxy, methylthio, methylsulfonyl, ethoxycarbonylmethoxy and vinyl groups and fluorine, chlorine and bromine atoms are preferred.

30 The alkyl, alkoxy and haloalkyl groups which may be substituted on the furyl or thienyl group, the 5-membered heterocyclic ring or the 6-membered heterocyclic ring represented by R_2 in formula (I) contain from 1 to 6 carbon atoms, preferably from 1 to 4 carbon atoms. Specific examples thereof include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, t-butoxy, trifluoromethyl, trifluoroethyl, trichloromethyl, and trichloroethyl groups. Among them, methyl, methoxy, ethoxy, and trifluoromethyl groups are preferred.

35 Examples of the halogen atom which may be substituted on the furyl or thienyl group, the 5-membered heterocyclic ring or the 6-membered heterocyclic ring represented by R_2 in formula (I) or which is contained in the haloalkyl group include fluorine, chlorine, bromine and iodine atoms.

Each of the compounds of the present invention, which is a novel one, can be prepared by the following method. Namely, a compound represented by formula (II):

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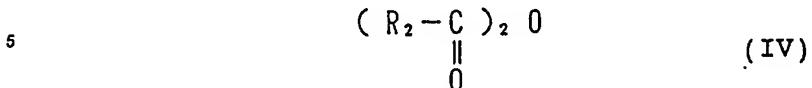
wherein R_1 represents the same meaning as defined above;
50 is reacted with a known acid halide compound represented by formula (III)

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wherein R_2 represents the same meaning as defined above; and
X represents a halogen atom;

or a known acid anhydride compound represented by the following formula:



wherein R₂ represents the same meaning as defined above.
In the production method as described above, the reaction is usually performed in the presence of an appropriate base. Examples of the base include organic bases such as triethylamine and pyridine and inorganic bases such as sodium methoxide, sodium hydride, potassium hydroxide, potassium carbonate and sodium hydrogencarbonate.

In the production method as described above, further, the reaction is performed either without using any solvent or in the presence of an inert solvent. Examples of usable solvents include hydrocarbons such as benzene and toluene, halogenated hydrocarbons such as chloroform and dichloroethane, ketones such as acetone and methyl ethyl ketone, ethers such as diethyl ether, tetrahydrofuran and dioxane and polar solvents such as N,N-dimethylformamide, dimethyl sulfoxide and acetonitrile.

In the production method as described above, the reaction temperature usually ranges from room temperature to the reflux temperature of the employed solvent. When it is required to shorten the reaction time, the reaction may be preferably carried out under heating.

The compound represented by formula (II), which is an intermediate in the production of the compound of formula (I) of the present invention, is also a novel compound according to the present invention and can be produced by the following method.

That is to say, 2-chloro-4-trifluoromethyl-5-thiazolecarboxylic acid (V), which can be synthesized by a known method as disclosed, for example, in J. Heterocyclic Chem., 22, 1621 (1985), is converted into an acid chloride derivative (VI) with the use of thionyl chloride and then reacted with aqueous ammonia to thereby give an amide derivative (VII). Then this compound (VII) is reacted with an appropriate dehydrating agent such as phosphorus oxychloride to thereby give 2-chloro-5-cyano-4-trifluoromethylthiazole (VIII). This compound (VIII) is then reacted with aqueous ammonia or various alkylamines in a solvent such as dioxane, tetrahydrofuran, N,N-dimethyl-formamide, dimethyl sulfoxide or acetonitrile. Thus the novel compound of formula (II) can be obtained.

The fungicide composition according to the present invention contains the thiazole derivative represented by formula (I) as an active ingredient. Since these thiazole derivatives are novel compounds, it is expected that they are effective on chemical-resistant strains. When the thiazole derivative of the present invention is to be used as an agricultural fungicide, the thiazole derivative can be mixed with various carriers and additives and formulated into various forms such as a wettable powder, an emulsifiable concentrate, a dust, granules or a flowable by techniques commonly employed in the production of agricultural chemicals. Furthermore, the thiazole derivative of the present invention is also usable as an industrial fungicide and bactericide. It exerts excellent antifungal activities on microorganisms belonging to the genus, for example, *Bacillus*, *Aspergillus*, *Penicillium* or *Saccharomyces*.

As a liquid carrier which can be used as a carrier to be employed in the agricultural fungicide composition according to the present invention, it may be selected from organic solvents commonly employed in the art, while as a solid carrier, it may be selected from clay minerals and pumice commonly employed in the art. In the formulation process, surfactants may be further added in order to impart emulsifiability, dispersibility or spreadability to the product. Furthermore, the fungicide may be blended with agricultural chemicals such as fertilizers, herbicides, insecticides or other fungicides.

In order to use as a fungicide, it is needed to apply the active ingredient in such an amount as to sufficiently achieve the desired effects. The application amount may range from 20 to 2,000 g/ha, and, in general, from 100 to 1,000 g/ha. The content of the active ingredient in the composition is adjusted to from 0.1 to 50 % by weight and the composition is formulated into a wettable powder, an emulsifiable concentrate, a dust, granules or a flowable.

An emulsifiable concentrate can be prepared by dissolving the active ingredient in an organic solvent usable for agricultural purposes and then adding an emulsifier soluble in the solvent. Examples of the solvent include xylene, o-chlorotoluene, cyclohexanone, isophorone, N,N-dimethylformamide, dimethyl sulfoxide and mixtures thereof. As particularly suitable solvents, mixtures of aromatic hydrocarbons, ketones and polar solvents may be cited. A surfactant may be used as an emulsifier in an amount of from 1 to 20 % by weight based on the emulsifiable concentrate. Either anionic, cationic or nonionic surfactants may be

used therefor. The concentration of the active ingredient may range from 0.5 to 50 % by weight, preferably from 5 to 30 % by weight.

Examples of the above-mentioned surfactant include anionic surfactants such as alkyl sulfuric esters, alkyl diphenyl ether disulfonates, naphthyl methanesulfonates, ligninsulfonates, alkyl sulfosuccinates, alkyl benzenesulfonates and alkyl phosphates; cationic surfactants such as alkylamine salts and quaternary ammonium salts; and nonionic surfactants such as polyoxyethylene alkyl ethers, polyoxyethylene aryl ethers, sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene sorbitol fatty acid esters, glycerol fatty acid esters and polyoxyethylene fatty acid esters.

A wettable powder may be prepared by adding the active ingredient to an inert finely pulverized solid carrier and a surfactant. In general, the content of the active ingredient ranges from 2 to 50 % by weight while the content of the surfactant ranges from 1 to 20 % by weight. As the inert finely pulverized solid carrier, native clay, silicates, silica and carbonates of alkaline earth metals may be used. Typical examples thereof include kaolin, ziegelite, talc, diatomaceous earth, magnesium carbonate, calcium carbonate and dolomite. As an emulsifier, a spreader or a dispersing agent to be used therein, commonly employed anionic surfactants, nonionic surfactants and mixtures thereof may be used. As the surfactants, those employed in the emulsifiable concentrate are usable in this instance.

A dust may be prepared by blending the active ingredient with an inert carrier commonly employed in the art, for example, talc, a fine powder of clay, pyrophyllite, diatomaceous earth or magnesium carbonate. The concentration of the active ingredient may range from 0.1 to 20 % by weight, preferably from 0.5 to 5 % by weight.

Granules may be prepared by mixing the active ingredient with an inert finely pulverized carrier, for example, bentonite, diatomaceous earth, kaolin, clay or talc, kneading the obtained mixture with water and then granulating the mixture with a granulating apparatus. Alternately, it may be prepared by adhering a solution of the active ingredient and a spreading agent to a granular carrier which have been previously prepared by granulation and the granular size thereof has been adjusted to a range of from about 15-to 30-mesh or mineral granules which have been previously prepared by grinding native pumice, acid clay or zeolite and the range of the granular size thereof has been adjusted. The concentration of the active ingredient in such granules ranges from 0.2 to 20 % by weight, preferably from 1 to 10 % by weight.

A flowable may be prepared by finely pulverizing the active ingredient and mixing it with a surfactant and water. As examples of the surfactant to be used here, the anionic surfactants, the cationic ones and the nonionic ones cited above regarding the emulsifiable concentrate may be used either alone or in a combination. The surfactant is generally mixed in an amount of from 1 to 20 % by weight, while the content of the active ingredient may range from 1 to 50 % by weight, preferably from 2 to 20 % by weight.

The compound according to the present invention represented by the above-mentioned formula (I) has an excellent antifungal activity and therefore exerts effects as an agricultural fungicide on disease damage of plants caused by over a wide range of microorganisms. For example, it exerts excellent preventive effects on tomato late blight, grape downy mildew, various powdery mildew, apple black spot, wheat and barley leaf rust, rice blast, rice sheath blight, various gray molds, rice bacterial grain rot and cucumber bacterial spot. Further, the compound according to the present invention exerts not only excellent preventive effects but also excellent therapeutic effects, which enables post-infective disease control.

Typical compounds according to the present invention are listed in Table 1. Each compound will be expressed in the compound No. given in Table 1 hereinafter.

TABLE 1

Compound No.	- R ₁	- R ₂	m.p. (°C)
1	- H		206~207
2	- H		198~199
3	- H		183~184
4	- H		216~217
5	- H		237~239
6	- H		233~234
7	- H		189~190
8	- H		159~160
9	- H		219~220
10	- H		263°C decomposed
11	- H		248~249

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TABLE 1 (CONT'D)

Compound No.	- R ₁	- R ₂	m.p. (°C)
12	- H		210~211
13	- H		138~139
14	- H		152~153
15	- H		128~129
16	- H		140~141
17	- H		166~167
18	- H		184~185
19	- H		180~181
20	- H		241~242
21	- H		205~206
22	- H		157~158

TABLE 1 (CONT'D)

Compound No.	- R ₁	- R ₂	m.p. (°C)
23	- H		185~186
24	- H		180~182
25	- H		188~189
26	- H		196~198
27	- H		156~157
28	- H		183~184
29	- H		169~171
30	- H		207~209
31	- H		203~205
32	- H		171~172
33	- H		124~125

TABLE 1 (CONT'D)

Compound No.	- R ₁	- R ₂	m.p. (°C)
34	- H		199~202
35	- H		117~118
36	- H		161~162
37	- H		207~208
38	- H		214~215
39	- H		182~183
40	- H		169~170
41	- H		117~118
42	- H		164~165
43	- H		164~165
44	- H		218~220

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TABLE 1 (CONT'D)

Compound No.	- R ₁	- R ₂	m.p. (°C)
45	- H		249~250
46	- H		174~175
47	- H		192~193
48	- CH ₃		98~99
49	- H		162~163
50	- H		138~139
51	- H		133~134
52	- H		128~129
53	- H		135~136
54	- H	- CH ₃	158~159
55	- H	- C ₂ H ₅	102~103

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TABLE 1 (CONT'D)

Compound No.	- R ₁	- R ₂	m.p. (°C)
56	- H	i - C ₃ H ₇ -	156~157
57	- H	n - C ₄ H ₉ -	106~107
58	- H	i - C ₄ H ₉ -	124~125
59	- H	t - C ₄ H ₉ -	141~142
60	- H	n - C ₅ H ₁₁ -	90~91
61	- H	n - C ₆ H ₁₃ -	79~80
62	- H	- CH ₂ CN	177~178
63	- H	- CH ₂ OCH ₃	97~98
64	- H	- CH ₂ CH ₂ COOC ₂ H ₅	116~117
65	- H		161~162
66	- H		179~181

TABLE 1 (CONT'D)

Compound No.	- R ₁	- R ₂	m.p. (°C)
67	- H	- CF ₃	260°C decomposed
68	- H		135~136
69	- H		161~162
70	- H		158~159
71	- H		
72	- H		209~210
73	- H		173~175
74	- H		194~195
75	- H		241~242
76	- H		216~217
77	- H		197~198

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TABLE 1 (CONT'D)

Compound No.	- R ₁	- R ₂	m.p. (°C)
78	- H		155~156
79	- H		128~129
80	- H		182~183
81	- H		194~195
82	- H		194~195
83	- H		205~206
84	- H		203~204
85	- H		241~242
86	- H		210~212
87	- H		220~221
88	- H		198~199

TABLE 1 (CONT'D)

Compound No.	- R ₁	- R ₂	m.p. (°C)
89	- H		129~130
90	- H		93~94
91	- H		161~162
92	- H		183~184

To further illustrate the present invention in greater detail, the following Examples (Synthesis Examples, Formulation Examples and Test Examples) will be given. However, it is to be understood that the present invention is not restricted thereto. Now typical synthesis examples of the present invention will be given.

SYNTHESIS EXAMPLE 1

30 Synthesis of 2-chloro-4-trifluoromethyl-5-thiazolecarbonyl chloride:

A 117.3 g portion of 2-chloro-4-trifluoromethyl-5-thiazolecarboxylic acid was dissolved in 1.1 l of dioxane. After adding 185 ml of thionyl chloride and a catalytic amount of N,N-dimethylformamide, the mixture was heated under reflux for 2.5 hours. Then the solvent was distilled off from the reaction mixture under reduced pressure. Thus 124.1 g of the target compound was obtained in the form of a colorless oily product. Yield = 98 %.

SYNTHESIS EXAMPLE 2

40 Synthesis of 2-chloro-4-trifluoromethyl-5-thiazolecarboxamide:

A 124.1 g portion of 2-chloro-4-trifluoromethyl-5-thiazolecarbonyl chloride was dissolved in 1.1 l of dioxane and added dropwise to 290 ml of 28 % aqueous ammonia at room temperature, followed by stirring at room temperature for 1 hour. After the completion of the reaction, the reaction mixture was neutralized with diluted hydrochloric acid, extracted with ethyl acetate, washed with water and an aqueous solution of common salt and dried over anhydrous magnesium sulfate. After distilling off the solvent under reduced pressure, the crude product thus obtained was recrystallized from a solvent mixture (toluene/hexane). Thus 98.5 g of the target compound was obtained. Yield = 86.1 %. m.p. = 89 - 90 °C.

50 SYNTHESIS EXAMPLE 3

Synthesis of 2-chloro-5-cyano-4-trifluoromethylthiazole:

A 43.3 g portion of 2-chloro-4-trifluoromethyl-5-thiazolecarboxamide was dissolved in 160 ml of N,N-dimethylformamide and 120 ml of phosphorus oxychloride was added dropwise thereto at 40 °C or below. After the completion of the addition, the resulting mixture was stirred at 70 °C for 3 hours. After the completion of the reaction, the reaction mixture was poured into ice-water, neutralized with sodium carbonate and extracted with ethyl acetate. The extract was washed with water and an aqueous solution of

common salt and dried over anhydrous magnesium sulfate. After distilling off the solvent under reduced pressure, 38.2 g of the target compound was obtained in the form of a colorless oily product. Yield = 95.7 %.

5 SYNTHESIS EXAMPLE 4

Synthesis of 2-amino-5-cyano-4-trifluoromethylthiazole:

A 1.0 g portion of 2-chloro-5-cyano-4-trifluoromethylthiazole was dissolved in 40 ml of tetrahydrofuran and 9 ml of 28 % aqueous ammonia was added dropwise thereto. After the completion of the addition, the resulting mixture was stirred at room temperature for 8 hours. After the completion of the reaction, the reaction mixture was poured into water, neutralized with diluted hydrochloric acid and extracted with ethyl acetate. The extract was washed with water and an aqueous solution of common salt and dried over anhydrous magnesium sulfate. After distilling off the solvent under reduced pressure, the crude product thus obtained was recrystallized from a solvent mixture (toluene/hexane) to thereby give 0.82 g of the target product. Yield = 90.3 %. m.p. = 166 - 167 °C.

SYNTHESIS EXAMPLE 5

20 Synthesis of 5-cyano-2-methylamino-4-trifluoromethylthiazole:

A 1.2 g portion of 2-chloro-5-cyano-4-trifluoromethylthiazole was dissolved in 40 ml of tetrahydrofuran and 1.32 g of a 40 % aqueous solution of methylamine was added dropwise thereto. After the completion of the addition, the resulting mixture was stirred at room temperature for 2 hours. After the completion of the reaction, the reaction mixture was poured into water, neutralized with diluted hydrochloric acid and extracted with ethyl acetate. The extract was washed with water and an aqueous solution of common salt and dried over anhydrous magnesium sulfate. After distilling off the solvent under reduced pressure, the crude product thus obtained was recrystallized from a solvent mixture (toluene/hexane) to thereby give 1.11 g of the target compound. Yield = 90.3 %. m.p. = 125 - 126 °C.

30 SYNTHESIS EXAMPLE 6

Synthesis of N-(5-cyano-4-trifluoromethylthiazol-2-yl)-4-chlorobenzamide (Compound No. 15):

35 A 0.2 g portion of 2-amino-5-cyano-4-trifluoromethylthiazole was dissolved in 30 ml of acetone and 0.2 g of 4-chlorobenzoyl chloride and 0.3 g of potassium carbonate were added thereto, followed by stirring at room temperature for 3 hours. After the completion of the reaction, the reaction mixture was poured into ice-water, extracted with ethyl acetate, washed with an aqueous solution of sodium carbonate, diluted hydrochloric acid, water and an aqueous solution of common salt and then dried over anhydrous magnesium sulfate. After distilling off the solvent under reduced pressure, the crude product thus obtained was purified by silica gel column chromatography. Thus 0.21 g of the target compound was obtained. Yield = 63.5 %. m.p. = 128 - 129 °C.

45 SYNTHESIS EXAMPLE 7

45 Synthesis of N-(5-cyano-4-trifluoromethylthiazol-2-yl)-propionamide: (Compound No. 55):

A 0.8 g portion of 2-amino-5-cyano-4-trifluoromethylthiazole was dissolved in 50 ml of dioxane and 0.8 ml of propionyl chloride and 1.2 ml of triethylamine were added thereto, followed by stirring at 60 °C for 6 hours. After the completion of the reaction, the reaction mixture was poured into ice-water, extracted with ethyl acetate, washed with an aqueous solution of sodium carbonate, diluted hydrochloric acid, water and an aqueous solution of common salt and dried over anhydrous magnesium sulfate. After distilling off the solvent under reduced pressure, the crude product thus obtained was purified by silica gel column chromatography. Thus 0.68 g of the target compound was obtained. Yield = 74.6 %. m.p. = 102 - 103 °C.

SYNTHESIS EXAMPLE 8

Synthesis of N-(5-cyano-4-trifluoromethylthiazol-2-yl)-trifluoroacetamide (compound No. 67):

5 A 0.8 g portion of 2-amino-5-cyano-4-trifluoromethylthiazole was dissolved in 50 ml of dioxane and 0.7 ml of trifluoroacetic anhydride and 0.7 ml of triethylamine were added thereto, followed by stirring at room temperature for 2 hours. After the completion of the reaction, the reaction mixture was poured into ice-water, extracted with ethyl acetate, washed with an aqueous solution of sodium carbonate, diluted hydrochloric acid, water and an aqueous solution of common salt and dried over anhydrous magnesium sulfate. After distilling off the solvent under reduced pressure, the crude product thus obtained was recrystallized from a solvent mixture (ethyl acetate/hexane) to thereby give 1.03 g of the target compound. Yield = 86.0 %. Decomposed at 260 °C.

SYNTHESIS EXAMPLE 9

15 Synthesis of N-(5-cyano-4-trifluoromethylthiazol-2-yl)-N-methyl-4-trifluoromethylbenzamide (Compound No. 48):

20 A 1.1 g portion of 5-cyano-2-methylamino-4-trifluoromethylthiazole was dissolved in 50 ml of dioxane and 1.6 ml of 4-trifluoromethylbenzoyl chloride and 1.5 ml of triethylamine were added thereto, followed by stirring at 60 °C for 2 hours. After the completion of the reaction, the reaction mixture was poured into ice-water, extracted with ethyl acetate, washed with an aqueous solution of sodium carbonate, diluted hydrochloric acid, water and an aqueous solution of common salt and dried over anhydrous magnesium sulfate. After distilling off the solvent under reduced pressure, the crude product thus obtained was recrystallized from a solvent mixture (toluene/hexane) to thereby give 1.10 g of the target compound. Yield = 54.1 %. m.p. = 98 - 99 °C.

SYNTHESIS EXAMPLE 10

30 Synthesis of N-(5-cyano-4-trifluoromethylthiazol-2-yl)-cyclopentanecarboxamide (Compound No. 66):

35 A 0.8 g portion of 2-amino-5-cyano-4-trifluoromethylthiazole was dissolved in 50 ml of dioxane and 1.2 g of cyclopentanecarbonyl chloride and 1.5 ml of triethylamine were added thereto, followed by stirring at 60 °C for 6 hours. After the completion of the reaction, the reaction mixture was poured into ice-water, extracted with ethyl acetate, washed with an aqueous solution of sodium carbonate, diluted hydrochloric acid, water and an aqueous solution of common salt and dried over anhydrous magnesium sulfate. After distilling off the solvent under reduced pressure, the crude product thus obtained was purified by silica gel column chromatography to thereby give 0.78 g of the target compound. Yield = 65.1 %. m.p. = 179 - 181 °C.

SYNTHESIS EXAMPLE 11

Synthesis of N-(5-cyano-4-trifluoromethylthiazol-2-yl)-1-naphtoamide (Compound No. 53):

45 A 0.7 g portion of 5-cyano-2-methylamino-4-trifluoromethylthiazole was dissolved in 40 ml of dioxane and 1.4 g of 1-naphthoyl chloride and 1.3 ml of triethylamine were added thereto, followed by stirring at 60 °C for 4 hours. After the completion of the reaction, the reaction mixture was poured into ice-water, extracted with ethyl acetate, washed with an aqueous solution of sodium carbonate, diluted hydrochloric acid, water and an aqueous solution of common salt, dried over anhydrous magnesium sulfate, and distilled under reduced pressure. The crude product thus obtained was recrystallized from a mixed solvent (toluene/hexane) to thereby give 0.78 g of the target compound. Yield = 62.0 %. m.p. = 135 - 136 °C.

SYNTHESIS EXAMPLE 12

55 Synthesis of N-(5-cyano-4-trifluoromethylthiazol-2-yl)-2-thiophencarboxamide (Compound No. 74):

A 0.7 g portion of 2-amino-5-cyano-4-trifluoromethylthiazole was dissolved in 40 ml of dioxane and 1.1 g of 2-thiophencarbonyl chloride and 1.3 ml of triethylamine were added thereto, followed by stirring at 60 °C

for 4 hours. After the completion of the reaction, the reaction mixture was poured into ice-water, extracted with ethyl acetate, washed with an aqueous solution of sodium carbonate, diluted hydrochloric acid, water and an aqueous solution of common salt, dried over anhydrous magnesium sulfate, and distilled under reduced pressure. The crude product thus obtained was purified by silica gel column chromatography to thereby give 1.13 g of the target compound. Yield = 81.3 %. m.p. = 194 - 195 °C.

SYNTHESIS EXAMPLE 13

10 Synthesis of N-(5-cyano-4-trifluoromethylthiazol-2-yl)-4-chloro-1-methyl-3-trifluoromethyl-5-pyrazolecarboxamide (Compound No. 79):

15 A 1.5 g portion of 2-amino-5-cyano-4-trifluoromethylthiazole was dissolved in 40 ml of pyridine and 3.8 g of 4-chloro-1-methyl-3-trifluoromethyl-5-pyrazolecarbonyl chloride was added thereto, followed by stirring at room temperature for 2 hours. After the completion of the reaction, the reaction mixture was poured into ice-water, extracted with ethyl acetate, washed with an aqueous solution of sodium carbonate, diluted hydrochloric acid, water and an aqueous solution of common salt, dried over anhydrous magnesium sulfate, and distilled under reduced pressure. The crude product thus obtained was purified by silica gel column chromatography to thereby give 1.86 g of the target compound. Yield = 70.5 %. m.p. = 128 - 129 °C.

20 SYNTHESIS EXAMPLE 14

Synthesis of N-(5-cyano-4-trifluoromethylthiazol-2-yl)-2-pyridinecarboxamide (Compound No. 83):

25 A 1.6 g portion of 2-amino-5-cyano-4-trifluoromethylthiazole was dissolved in 30 ml of pyridine and 3.5 g of 2-pyridinecarbonyl chloride was added thereto, followed by stirring at room temperature for 2 hours. After the completion of the reaction, the reaction mixture was poured into ice-water, extracted with ethyl acetate, washed with diluted hydrochloric acid, water and an aqueous solution of common salt, dried over anhydrous magnesium sulfate, and distilled under reduced pressure. The crude product thus obtained was purified by silica gel column chromatography to thereby give 1.42 g of the target compound. Yield = 57.5 %, m.p. = 205 - 206 °C.

SYNTHESIS EXAMPLE 15

35 Synthesis of N-(5-cyano-4-trifluoromethylthiazol-2-yl)-3-chloro-5-trifluoromethyl-2-pyridinecarboxamide (Compound No. 90):

40 A 0.8 g portion of 2-amino-5-cyano-4-trifluoromethylthiazole was dissolved in 30 ml of dioxane and 1.0 g of 3-chloro-5-trifluoromethyl-2-pyridinecarbonyl chloride and 0.6 ml of triethylamine were added thereto, followed by stirring at 60 °C for 3 hours. After the completion of the reaction, the reaction mixture was poured into ice-water, extracted with ethyl acetate, washed with diluted hydrochloric acid, water and an aqueous solution of common salt, dried over anhydrous magnesium sulfate, and distilled under reduced pressure. The crude product thus obtained was purified by silica gel column chromatography to thereby give 0.98 g of the target compound. Yield = 59.0 %. m.p. = 93 - 94 °C.

45 SYNTHESIS EXAMPLE 16

Synthesis of N-(5-cyano-4-trifluoromethylthiazol-2-yl)-2-pyrazinecarboxamide (Compound No. 92):

50 A 1.2 g portion of 2-amino-5-cyano-4-trifluoromethylthiazole was dissolved in 30 ml of pyridine and 1.8 g of 2-pyrazinecarbonyl chloride was added thereto, followed by stirring at room temperature for 4 hours. After the completion of the reaction, the reaction mixture was poured into ice-water, extracted with ethyl acetate, washed with diluted hydrochloric acid, water and an aqueous solution of common salt, dried over anhydrous magnesium sulfate, and distilled under reduced pressure. The crude product thus obtained was purified by silica gel column chromatography to thereby give 1.56 g of the target compound. Yield = 83.9%. m.p. = 183 - 184 °C.

Next, the compositions of the present invention will be described in greater detail by citing a formulation example for each type.

FORMULATION EXAMPLE 1 (Emulsifiable Concentrate)		
	Component	Amount (parts by weight)
5	Compound No. 12	20
	o-Chlorotoluene	40
	Cyclohexanone	35
	Sorpol 900 B	5
10	(Sorpol 900 B: a trademark of a product comprising a polyoxyethylenealkylphenol polymer, a polyoxyethylene alkylaryl ether, a polyoxyethylene sorbitan fatty acid ester and an anionic surfactant; manufactured by Toho Chemical Industry Co., Ltd.)	

These components were uniformly mixed and dissolved to thereby give an emulsifiable concentrate according to the present invention.

15

FORMULATION EXAMPLE 2 (Wettable Powder)		
	Component	Amount (parts by weight)
20	Compound No. 4	25
	Kaolin clay	57
	Sorpol 5039	9
	Sorpol 5060	9
25	(Sorpol 5039: a trademark of a product comprising an ammonium polyoxyethylene alkylaryl ether sulfate; Sorpol 5060: a trademark of a product comprising a sodium alkylallylsulfonate and phosphoric acid; each manufactured by Toho Chemical Industry Co., Ltd.)	

These components were mixed and ground to thereby give a wettable powder according to the present invention.

30

FORMULATION EXAMPLE 3 (Dust)		
	Component	Amount (parts by weight)
35	Compound No. 19	5
	Kaolin clay	95

40 These components were mixed and ground to thereby give a dust according to the present invention.

40

FORMULATION EXAMPLE 4 (Granule)		
	Component	Amount (parts by weight)
45	Compound No. 46	6
	Bentonite	44
	Talc	44
50	Sodium ligninsulfonate	6

These components were uniformly mixed and ground. After adding water, the mixture was kneaded, granulated and dried to thereby give granules according to the present invention.

55

FORMULATION EXAMPLE 5 (Flowable)	
Component	Amount (parts by weight)
Compound No. 24	10
Ethylene glycol	6
Sorpol 3078	6
Sorpol 7512	— 1
Water	77

(Sorpol 3078: a trademark of a product comprising a polyoxyethylene alkylphenyl ether sulfate; Sorpol 7512: a trademark of a product; each manufactured by Toho Chemical Industry Co., Ltd.)

These components were uniformly mixed and ground to thereby give a flowable according to the present invention.

FORMULATION EXAMPLE 6 (Emulsifiable Concentrate)	
Component	Amount (parts by weight)
Compound No. 38	10
Isophorone	22
o-Chlorotoluene	28
Xylene	22
Sorpol 900A	9
Sorpol 900B	9

(Sorpol 900 A: a trademark of a product comprising a polyoxyethylenealkylphenol polymer, a polyoxyethylene alkylaryl ether, a polyoxyethylene sorbitan fatty acid ester and an anionic surfactant; manufactured by Toho Chemical Industry Co., Ltd.)

These components were uniformly mixed and dissolved to thereby give an emulsifiable concentrate according to the present invention.

To further illustrate the preventive effects of the compounds of the present invention on fungi, the following Test Examples will be given.

TEST EXAMPLE 1

40 Test of preventive effect on rice blast:

Rice plants (variety: *koshihikari*) were cultivated in plastic pots (diameter: 7 cm). At the difoliate stage, 10 ml portions of test compound solutions comprising 100 ppm of the test compositions prepared in accordance with the above Formulation Example 1 were sprayed with the use of a spray gun. Regarding each test compound, four lots each having 10 plants were employed, and two of them were treated with the test compound (test lot), and the other two of them were not treated with the test compound (control lot). One day after the treatment with the composition, each rice plant was inoculated with a conidium suspension of *Pyricularia oryzae* which causes rice blast. After the completion of the inoculation, the rice plants were cultivated under moisture-saturation at 25°C in the dark for 24 hours followed by at 25°C for 6 days with 12-hour photoperiod. On the 7th day after the inoculation, the lesions of the first and second leaves were examined and the preventive value was calculated in accordance with the following Equation (1). Table 2 summarizes the results.

Equation (1):

$$5 \quad \text{Prevention value} = \frac{(\text{Lesions of control lot}) - (\text{Lesions of test lot})}{(\text{Lesions of control lot})} \times 100$$

10

TABLE 2

15

(Preventive effect on rice blast)	
Compound No.	Preventive value
2	100
6	100
9	100
12	100
19	100
24	100
31	100
36	100
41	100
43	100
47	100
49	100
54	100
56	100
57	100
59	100
63	100
66	100
68	100
84	100
90	100

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25

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40 TEST EXAMPLE 2

Test of preventive effect on wheat powdery mildew:

45 Wheat plants (variety: *norin No. 61*) were cultivated in plastic pots (diameter: 7 cm). At the difoliate stage, 10 ml portions of test compound solutions comprising 100 ppm of the test compositions prepared in accordance with the above Formulation Example 2 were sprayed with the use of a spray gun. Regarding each test compound, four lots each having 13 plants were employed, and two of them were treated with the test compound (test lot), whereas the other two of them were not treated with the test compound (control lot). One day after the treatment with the composition, each wheat plant was inoculated with a conidium suspension of *Erysiphe graminis* which causes wheat powdery mildew. After the completion of the inoculation, the wheat plants were cultivated at 20°C in the dark for 12 hours followed by at 20°C for 6 days with 12-hour photoperiod. On the 7th day after the inoculation, the rate of the lesions of the first and second leaves were examined, and the preventive value was calculated in accordance with Equation (1). Table 3 summarizes the results.

55

TABLE 3

(Preventive effect on wheat powdery mildew)		
	Compound No.	Preventive value
5	1	100
	4	100
10	13	100
	17	100
15	32	100
	55	100
	58	100
	60	100
	65	100
	67	100

TEST EXAMPLE 3

20 Test of preventive effect on wheat leaf rust:

Wheat plants (variety: *norin No. 61*) were cultivated in plastic pots (diameter: 7 cm). At the difoliate stage, 10 ml portions of test compound solutions comprising 100 ppm of the test compositions prepared in accordance with the above Formulation Example 6 were sprayed with the use of a spray gun. Regarding each test compound, four lots each having 13 plants were employed, and two of them were treated with the test compound (test lot), whereas the other two of them were not treated with the test compound (control lot). One day after the treatment with the composition, each wheat plant was inoculated with a conidium suspension of *Puccinia recondita* which causes wheat leaf rust. After the completion of the inoculation, the wheat plants were cultivated under moisture-saturation at 20 °C in the dark for 24 hours followed by at 20 °C for 6 days with 12-hour photoperiod. On the 7th day after the inoculation, the rate of the lesions of the first and second leaves were examined, and the preventive value was calculated in accordance with Equation (1). Table 4 summarizes the results.

TABLE 4

(Preventive effect on wheat leaf rust)		
	Compound No.	Preventive value
40	23	100
	27	100
45	28	100
	30	100
	80	100

TEST EXAMPLE 4

50 Test of preventive effect on wheat glume blotch:

Wheat plants (variety: *norin No. 61*) were cultivated in plastic pots (diameter: 7 cm). At the difoliate stage, 10 ml portions of test compound solutions comprising 200 ppm of the test compositions prepared in accordance with the above Formulation Example 5 were sprayed with the use of a spray gun. Regarding each test compound, four lots each having 13 plants were employed, and two of them were treated with the test compound (test lot), whereas the other two of them were not treated with the test compound (control lot). One day after the treatment with the composition, each wheat plant was inoculated with a conidium suspension of *Leptosphaeria nodorum* which causes wheat glume blotch. After the completion of the

inoculation, the wheat plants were cultivated under moisture-saturation at 20°C in the dark for 48 hours followed by at 20°C for 6 days with 12-hour photoperiod. On the 7th day after the inoculation, the rate of the lesions of the first and second leaves were examined, and the preventive value was calculated in accordance with Equation (1). Table 5 summarizes the results.

5

TABLE 5

(Preventive effect on wheat glume blotch)		
	Compound No.	Preventive value
10	48	100
	53	100
	70	100

15

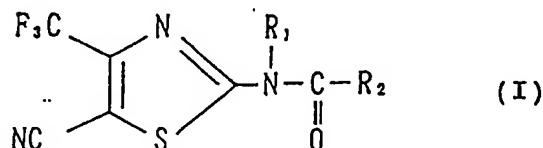
The compounds of the present invention, which are novel ones, are highly usable as an agricultural fungicide and an industrial fungicide.

While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one of ordinary skilled in the art that various changes and modifications can be made 20 without departing from the spirit and scope thereof.

Claims

1. A thiazole derivative represented by the following formula (I):

25



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wherein R₁ represents a hydrogen atom or an alkyl group; and R₂ represents a phenyl group, a substituted phenyl group, a benzyl group, a substituted benzyl group, a phenylalkyl group, a naphthyl group, an alkyl group, a cycloalkyl group, a substituted alkyl group, an alkenyl group, an alkynyl group, a furyl group, a thieryl group, a 5-membered heterocyclic ring containing 1 to 3 nitrogen atoms in the ring and a 6-membered heterocyclic ring containing 1 to 3 nitrogen atoms in the ring; provided that when the 5-membered heterocyclic ring or the 6-membered heterocyclic ring contains one or two nitrogen atom, the remaining atoms in the ring are all carbon atoms or a combination of carbon atoms with one oxygen atom or one sulfur atom; and further provided that the furyl group, the thieryl group, the 5-membered heterocyclic ring and the 6-membered heterocyclic ring may be substituted by one to three substituents selected from an alkyl group, an alkoxy group, a halogen atom and a haloalkyl group.

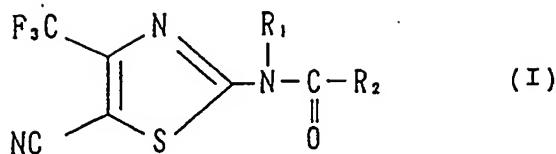
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2. The thiazole derivative of claim 1, which is selected from N-(5-cyano-4-trifluoromethylthiazol-2-yl)-4-chlorobenzamide, N-(5-cyano-4-trifluoromethylthiazol-2-yl)-propionamide, N-(5-cyano-4-trifluoromethylthiazol-2-yl)-trifluoroacetamide, N-(5-cyano-4-trifluoromethylthiazol-2-yl)-N-methyl-4-trifluoromethylbenzamide, N-(5-cyano-4-trifluoromethylthiazol-2-yl)-cyclopentanecarboxamide, N-(5-cyano-4-trifluoromethylthiazol-2-yl)-1-naphtoamide, N-(5-cyano-4-trifluoromethylthiazol-2-yl)-2-thiophenecarboxamide, N-(5-cyano-4-trifluoromethylthiazol-2-yl)-4-chloro-1-methyl-3-trifluoromethyl-5-pyrazolecarboxamide, N-(5-cyano-4-trifluoromethylthiazol-2-yl)-2-pyridinecarboxamide, N-(5-cyano-4-trifluoromethylthiazol-2-yl)-3-chloro-5-trifluoromethyl-2-pyridinecarboxamide, N-(5-cyano-4-trifluoromethylthiazol-2-yl)-2-pyrazinecarboxamide.

55

3. A fungicide composition comprising a thiazole derivative represented by the following formula (I):

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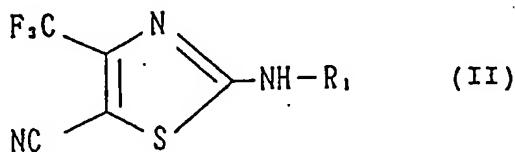
10 wherein R₁ represents a hydrogen atom or an alkyl group; and R₂ represents a phenyl group, a substituted phenyl group, a benzyl group, a substituted benzyl group, a phenylalkyl group, a naphthyl group, an alkyl group, a cycloalkyl group, a substituted alkyl group, an alkenyl group, an alkynyl group, a furyl group, a thieryl group, a 5-membered heterocyclic ring containing 1 to 3 nitrogen atoms in the ring and a 6-membered heterocyclic ring containing 1 to 3 nitrogen atoms in the ring; provided that when the 5-membered heterocyclic ring or the 6-membered heterocyclic ring contains one or two nitrogen atom, the remaining atoms in the ring are all carbon atoms or a combination of carbon atoms with one oxygen atom or one sulfur atom; and further provided that the furyl group, the thieryl group, the 5-membered heterocyclic ring and the 6-membered heterocyclic ring may be substituted by one to three substituents selected from an alkyl group, an alkoxy group, a halogen atom and a haloalkyl group; and a carrier.

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4. A compound represented by the following formula (II):

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wherein R₁ represents a hydrogen atom or an alkyl group.

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European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 93 10 6230

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	US-A-4 324 899 (MARK D.FRISHBERG) * claim 1 *	4	C07D277/56 C07D417/12 A01N43/78
A	EP-A-0 384 211 (BAYER AG.) * page 25, line 33 - page 27, column 14; claims 17-9 *	1,3	
A	EP-A-0 328 954 (BAYER AG.) * claims 1,5-8 *	1,3	
A	US-A-2 726 247 (EDMUND B. TOWNE ET AL) * claims *	1,4	

The present search report has been drawn up for all claims			
Place of search	Date of compilation of the search	Examiner	
THE HAGUE	30 JUNE 1993	HENRY J.C.	
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	